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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,588	05/03/2001	Stephen Friend	215538.00108	7335

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,588	FRIEND ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10-13 and 15-46* is/are pending in the application.

4a) Of the above claim(s) *21,22 and 26-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10-13,15-20 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/15/02, 6/25/02, 3/16/04 & 5/17/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Receipt is acknowledged of an amendment, filed 10/27/2004, in which several claims were amended (claims 1-3, 10-11, 18) and in which claims were cancelled (claims 8-9, 14). Claims 1-7, 10-13 and 15-46 are pending in the instant application, with claims 21-22 and 26-46 withdrawn from consideration as being directed to nonelected subject matter.

Any rejection of record not addressed herein is withdrawn. This action is not final as there are new grounds of rejection presented herein that were not necessitated by applicants' amendment of the claims in the response filed on 10/27/2004.

Information Disclosure Statement (IDS)

Receipt is acknowledged of information disclosure statements filed on 4/15/2002, 6/25/2002, 7/8/2003, 3/16/2004 and 5/17/2004. The documents associated with the IDS filed on 4/15/2002 have been located and are now part of the file. All references cited on each IDS have been considered. Duplicate references have been lined through in order to avoid duplicate printing on the face of any patent that issues from the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 12-13, 18-20 & 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is vague and indefinite in that the metes and bounds of the phrase "analogous or homologous to a defect found in a human tumor" are unclear. **This rejection is maintained for reasons of record and repeated here.** It is also unclear the degree of sequence identity or functional similarity required for a gene defect to be "analogous" or "homologous" to another gene defect found in human tumors.

Claim 12 is vague and indefinite in that the metes and bounds of the terms mammalian "analog" or "homolog" are unclear. **This rejection is maintained for reasons of record and repeated here.** These terms are not clearly defined in the specification and are open to interpretation by the individual practitioner.

Likewise, claim 18 is vague and indefinite in that the metes and bounds of the phrase "an altered gene that is analogous or homologous to a primary tumor defect". The terms "analogous" or "homologous" are subjective in nature and not clearly defined in the instant specification in a limiting manner. **This is a new rejection.**

Response to Arguments

Applicant's arguments filed 10/27/2004 have been fully considered but they are not persuasive. The response essentially argues that the terms "analagous" and "homologous" are defined in the specification, citing passages at page 12. The specification defines the term homologous as "Two nucleic acid molecules are determined to be homologous if their nucleic acid sequences share a similarity of greater than 40% as determined by HASH-coding

algorithms." It is argued that the specification also states that homologous genes have a direct relationship among a family of genes in which certain sequences or domains are strongly conserved among the family members and provides examples of homologs (e.g. yeast mec 1 and the human AT-related kinase). Thus, it is argued, the specification provides the requisite degree of sequence similarity and functional similarity. It is further argued that the term "analogous" is defined at page 12 as referring to genes that are not related (i.e. do not have conserved sequences), but which have similar functions.

In particular, the argument with regard to the term "analogous" is not persuasive. How similar in function do two gene products have to be in function for them to be considered "analogous" in function? This is not defined in the specification and is a subjective determination that is open to interpretation by the skilled artisan, making unclear whether or not one has infringed the claimed invention. With regard to the term "homologous", the language concerning "greater than 40%" similarity would be useful for setting a minimal level of identity, the specification gives additional definitions of what might satisfy the limitations of the term and does not specify that *each* definition must be satisfied in order to meet the limitation of being "homologous" genes. Thus, the skilled artisan does not know which definition to apply. For example, would a gene from yeast that has 38% identity to a human gene and encodes a protein that has a catalytic domain that is 45% identical to the human protein's catalytic domain necessarily qualify as a "homolog" of the human gene? Even if one accepts that all of the criteria recited on page 12 must be met, what determines whether the yeast gene in such a case, even if it had 40% identity to the human gene, has a "direct relationship among a family of

genes"? Again, how similar in function do the two gene products have to be in order for the genes encoding them to be considered as "homologs"?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 10-13, 15-20 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for synthetic lethal screens in genetically tractable organisms as defined in the specification (*Saccharomyces cerevisiae*, *Schizzosaccaromyces pombe*, *Caenorhabditis elegans* or *Drosophila melanogaster*), does not reasonably provide enablement for synthetic lethal screens in other model systems (e.g. insect or mammalian cells, vertebrate animals, etc.) and specifically does not provide enablement for use of the elected embodiment (i.e. p53) as the primary gene defect in any of the genetically tractable organisms identified in the specification (i.e. *Saccharomyces cerevisiae*, *Schizzosaccaromyces pombe*, *Caenorhabditis elegans* or *Drosophila melanogaster*). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. **This is a new rejection.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The invention is complex, involving the use of a primary genetic defect as a genetic background for the selection of mutations at secondary sites that render the combination of genetic defects lethal to the particular host cell type. The identity of the gene comprising the secondary gene defect that proves lethal is then determined. Such identified secondary-lethal genes are potential secondary drug targets for cells comprising the primary gene defect (e.g. tumor cells). In each instance, the process requires a model system that is genetically tractable. For instance, the skilled artisan needs to be able to effect the secondary mutations in such a way that one is able to perform a lethal screen and still be able to identify those secondary mutations that render the host cell nonviable (e.g. replica plating in genetically tractable organisms such as yeast or bacteria).

Breadth of the claims: The breadth of the claims exacerbates the complexity of the invention. In the broadest claims, the primary gene defect can include a defect in literally any gene in the host cell genome and includes literally any organism (e.g. prokaryotic cells, yeast and multicellular organisms). In certain claims (e.g. claim 10), it is specified that a particular gene or gene family member is necessarily the site where the secondary mutation is effected (i.e. secondary mutations are made at a particular locus rather than randomly throughout the genome). In each case, the claims encompass a huge genus of a *combination* of primary and secondary mutations that, together, must be lethal to the cell. This is particularly problematic for the claims where the site of the secondary mutation is specified. For claims 18-20, 23-25, it is specified that the synthetic lethal screen is performed in a genetically tractable organism that comprises a gene that is analogous or homologous to a primary tumor defect. For the elected embodiment, where the primary gene defect is p53, this requires that a homolog or analog of p53 be known in the art

at the time of filing for the specifically recited organisms (i.e. *Saccharomyces cerevisiae*, *Schizzosaccaromyces pombe*, *Caenorhabditis elegans* or *Drosophila melanogaster*).

Guidance of the specification/ The existence of working examples: The instant specification teaches that, "The current state of human cell genetics does not permit one to exploit genetics for drug discovery, so it is necessary to use "model organisms" for which genetic manipulation is facile" (page 15, lines 15-17). The specification only teaches working examples of actual synthetic lethal screens in the yeast *S. cerevisiae*, however. While a working example is provided for *Drosophila melanogaster*, it does not feature the isolation of secondary mutations that actually prove lethal to the organism (e.g. Example 7). In the view of the applicants, the presence of secondary mutations that enhance or make worse a "rough eye" phenotype in *D. melanogaster* is the "conceptual equivalent" of synthetic lethal mutations (e.g. page 29, lines 17-21). This interpretation of the term "synthetic lethal" is not consistent with the art and is not consistent with what is actually claimed, where secondary lethal mutants are identified. The specification comprises a single, general statement regarding the use of higher organisms for synthetic lethal screens. At page 15, lines 26-29, it is suggested that gene knockouts in murine embryonic stem cells may be useful for genetic analysis, but the specification provides no further guidance on how to do genetic lethal screens in higher order organisms than the specifically recited genetically tractable organisms (i.e. *Saccharomyces cerevisiae*, *Schizzosaccaromyces pombe*, *Caenorhabditis elegans* or *Drosophila melanogaster*). The specification provides no guidance as to what are the p53 genes, or their homologs or analogs, in *Saccharomyces cerevisiae*, *Schizzosaccaromyces pombe*, *Caenorhabditis elegans* or *Drosophila melanogaster*.

State of the art/Predictability of the art: The prior art does not appear to teach how one would perform a synthetic lethal screen in organisms other than *S. cerevisiae*, *S. pombe*, *C. elegans* or *D. melanogaster*. The prior art does not teach that a p53 gene had been identified in any of the genetically tractable organisms specifically recited in the specification at the time of filing. Nor does the prior art teach the identification of an analog or homolog of p53 in any of these organisms. For these reasons, the prior art does not offset the deficiencies of the instant specification with regard to practicing the claimed invention in organisms other than *S. cerevisiae*, *S. pombe*, *C. elegans* or *D. melanogaster*. Nor does the prior art offset the deficiencies of the instant specification with regard to practicing the claimed invention in *S. cerevisiae*, *S. pombe*, *C. elegans* or *D. melanogaster* with p53, or its homolog or analog, as part of the primary genetic defect. In fact, Buchman et al (U.S. 2004/0161827 A1, effective filing date of 3/16/1999) teach that only two invertebrate homologs of p53 had been identified prior to their invention, in mollusc and squid (paragraph 005).

The amount of experimentation necessary: Given the combination of factors outlined above, particularly the lack of guidance from the prior art concerning how to isolate secondary genetic mutations that prove lethal to higher order organisms (e.g. mice, humans, etc.) that are not genetically tractable, and the fact that p53 genes, or their homologs or analogs, had not been identified at the time of filing for the specifically recited genetically tractable organisms, it would have required undue, unpredictable experimentation to practice the claimed invention (i) in organisms other than *S. cerevisiae*, *S. pombe*, *C. elegans* or *D. melanogaster*, and (ii) in *S. cerevisiae*, *S. pombe*, *C. elegans* or *D. melanogaster* with p53 or its analog or homolog (i.e. the elected embodiment). Therefore, the instant application is found to be enabling only for those

embodiments directed to the genetically tractable organisms *S. cerevisiae*, *S. pombe*, *C. elegans* or *D. melanogaster* where the primary defect is not in p53, or its analog or homolog.

Conclusion

No claims are allowed. This action is not final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

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PRIMARY EXAMINER

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